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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,157	08/16/2001	Hiroo Imura	299002032411	2951

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	14

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,157	IMURA ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-39* is/are pending in the application.

4a) Of the above claim(s) *23-34,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/121,446*.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 10 April 2003 (Paper No. 13) has been entered in full. Claims 35 and 36 have been amended. Claims 23-34 and 38-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Claims 35, 36, and 37 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The objection to the specification as set forth at pp. 3 ¶6 of the previous Office Action (Paper No. 12, 16 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 10 April 2003).

4. The objection to claims 35 and 36 as set forth at pp. 3 ¶7 of the previous Office Action (Paper No. 12, 16 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 10 April 2003).

New Objections

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figures 1 and 2 contain subsections A-E. A proposed drawing correction, corrected drawings, or amendment to the

specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims **35** and **36** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicant refers to the amino acid sequence of SEQ ID NO: 2 in claims 35 and 36. It is unclear as to what the Applicant considers the invention as SEQ ID NO: 2 is a nucleic acid sequence.

Maintained Objections And/Or Rejections

7. Claims **35, 36,** and **37** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth in at pp. 3-6 ¶8-14 of the previous Office Action (Paper No. 12, 16 January 2003).

8. The Applicant traverses the 35 U.S.C. §112 ¶1 of claims 35, 36, and 37 as set forth in at pp. 3-6 ¶8-14 of the previous Office Action (Paper No. 12, 16 January 2003) on the grounds that: **(a)** since SEQ ID NO: 1 is novel, no related diseases had been characterized as of the filing

date of the instant application, nevertheless the invention is drawn to any disease that may be characterized after the filing date to have abnormal endothelin receptor (SEQ ID NO: 1) activity, **(b)** it would be routine to screen for compounds that agonize/antagonize SEQ ID NO: 1 activity, **(c)** any compound identified in the screening method component of claims 35, 36, and 37 would be expect to work on an appropriate SEQ ID NO: 1 related disorder, **(d)** the Examiner is fundamentally incorrect as the nexus between the compound and the disease state is SEQ ID NO: 1 itself and that the condition is characterized by abnormal endothelin receptor activity therefore any compound normalizing endothelin receptor activity would normalize the condition, **(e)** Evidentiary Exhibits A1-A10, and **(f)** Exhibit B. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

9. The Examiner maintains the rejection under 35 U.S.C. §112 ¶1 of claims 35, 36, and 37.

10. In regards to "**(a)**", since no disease is known, no guidance can be offered to the skilled artisan to how or why a treatment directed to SEQ ID NO: 1 should be undertaken. Thus an undue burden of experimentation is placed on the skilled artisan to first identify a disease or disorder related to abnormal SEQ ID NO: 1 activity, evaluate the role of SEQ ID NO: 1 in the disease or disorder, and then determine a treatment protocol. For example, MacCumber et al. (March 1990) "*Endothelin in brain: Receptors, mitogenesis, and biosynthesis in glial cells.*" Proc. Natl. Acad. Sci. USA **87**: 2359-2363 (**IDS**) teaches that endothelin, a potent vasoconstrictor with several isoforms, acts on smooth muscle, stimulates the growth of smooth muscle cells, and fibroblasts. In addition, MacCumber et al. (1990) teaches that endothelin also is active in the central nervous system enhancing inositolphospholipid turnover in glia and stimulating glial growth (pp. 2359). From this reference it is evident that endothelin receptors

can have activity in different organ systems and have differing effects. Thus without guidance or examples, the level of uncertainty is daunting and thus impedes a reasonable expectation of success to use the claimed invention.

11. Concerning **"(b)"**, while the Examiner accepts that the screening protocol contained in claims 35, 36, and 37 could be practiced, no motivation or reasonable expectation of success exists to fulfill the treatment as set forth in the preamble of claim 35. Martin et al. (1990) "*Heterogeneity of Cell Surface Endothelin Receptors.*" The Journal of Biological Chemistry **265**(23): 14044-14049 **(IDS)** teaches that endothelin receptors differ in their pharmacological activities such as ligand affinity, presenting a degree of unpredictability (Table 1; Figure 6). Thus due to a lack of guidance, burden of experimentation, and uncertainty in the utility of any given ligand to have the desired therapeutic effect on SEQ ID NO: 1 if and when an applicable disease or disorder is identified and characterized.

12. On **"(c)"**, antagonistic and/or agonistic activity or properties in vitro is no guarantee of activity in vivo or therapeutic benefit. Simonson et al. (1990) "*Cellular Signaling by peptides of the endothelin gene family.*" FASEB Journal **4**(12): 2989-3000 offers an outline of the intracellular signaling pathways of endothelin receptors and teaches the endothelin receptors are involved in numerous biological activities (pp. 2991). Further a large number of vasoactive hormones act on the endothelin receptor family which vary in effect and may or may not be considered therapeutic (Table 1). Therefore, the skilled artisan is confronted with a level of unpredictability for the action of any given ligand of SEQ ID NO: 2 and an unknown activity *in vitro* and *in vivo* which requires undue experimentation to characterize.

13. In response to **"(d)"**, the Examiner maintains that no nexus between any known disease or disorder and SEQ ID NO: 1 or SEQ ID NO: 2 exists. While it is accepted that certain diseases and disorders are related to endothelin receptors, the claims are directed to the nucleic acids SEQ ID NO: 1 and SEQ ID NO: 2 which encode a novel endothelin receptor. To date, no evidence exists to suggest to or convince a skilled artisan that SEQ ID NO: 1 or SEQ ID NO: 2 play any role in any disease or disorder and therefore no motivation or reasonable expectation of success is present for the instant invention.

14. Furthermore the Applicant asserts that any compound which "normalizes" "abnormal endothelin activity" would "normalize" the activity of SEQ ID NO: 1 or SEQ ID NO: 2 downstream and therefore "normalize" the condition.

15. Firstly, the Applicant has failed to define what is meant by abnormal SEQ ID NO: 1 or SEQ ID NO: 2 activities or what "normalizing" said activity entails. No guidance is given nor any working examples to offer support to this assertion.

16. Secondly, no expectation is reasonable that an as of yet undefined normalization of an unknown abnormal activity will have any effect on the "biological pathways downstream from the receptor." As noted in the previous Office Action, endothelin receptors are involved in a broad range of activities and it is not clear as to what biological pathways downstream from the receptor the Applicant is referring. For instance, Maggi et al. (1991) "*Immunolocalization, binding, and biological activity of endothelin in rabbit uterus: effect of ovarian steroids.*" American Journal of Physiology **260** (2, Pt. 1): E292-E305 teaches that endothelin receptors play a role in the reproductive endocrine cycle. The endothelin receptors respond to a variety of ligands and are a part of complex system; therefore it is difficult to predict what effect any given

ligand would have on the biological pathways downstream of the endothelin receptors (pp. E302-E305).

17. Finally, since there is no definition, guidance, examples, known diseases, defined activity, defined correction of known abnormal activity, the skilled artisan would have to undertake the following tasks: first to identify a ligand, to identify a SEQ ID NO: 1 or SEQ ID NO: 2 related disorder, and then to determine, through trial and error, a ligand with a therapeutic effect. Not withstanding the determination of a ligand which may administered to a patient with acceptable side effects remains the questions of the treatment regiment such as dosage, administration route, appropriate carriers, and target (i.e. cell, tissue, or organ).

18. On **"(e)" or Evidentiary Exhibits A1-A10**, the structure and activity of ET_A and its ligands are of no relevance to the instant application. The Examiner accepts that known ligands and known endothelin receptors have therapeutic value. However, the grounds of this rejection are that neither SEQ ID NO: 1 nor SEQ ID NO: 2 are related to no known diseases or disorders, both are of unknown biological relevance, and unknown physiological significance.

19. In regard to **"(f)" or Exhibit B**, the structure and activity of bosentan is of no relevance to the instant application. The Examiner accepts that known ligands and known endothelin receptors have therapeutic value. However, the grounds of this rejection are that neither SEQ ID NO: 1 nor SEQ ID NO: 2 are related to no known diseases or disorders, both are of unknown biological relevance, and unknown physiological significance.

20. Finally, regarding SEQ ID NO: 1 and SEQ ID NO: 2 related conditions, the art recognizes that altered levels of endothelin are found in ischemic heart disease, advanced atherclerosis, Buerger's disease, Raynaud's phenomenon, pulmonary hypertension, and patients

undergoing surgical procedures such as percutaneous transluminal coronary angioplasty (US 6432994 Col. 4 lines 34-53). However, neither the specification nor the art discloses a correlation between a specific disease and an abnormal activity of the ET receptors encoded by SEQ ID NO: 1 or SEQ ID NO: 2, which is what the claims require. Due to the large quantity of experimentation necessary to evaluate all the possible endothelin receptor-related conditions, the lack of direction/guidance presented in the specification which endothelin receptor-related conditions, the absence of working examples directed to endothelin receptor-related conditions, the complex nature of the invention, the unpredictability of the effects of test compounds on a endothelin receptor-related condition (US 6432994), and the breadth of the claims which fail to recite limitations for which endothelin receptor-related condition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

21. Therefore the rejection of claims 35, 36, and 37 under 35 U.S.C. §112 ¶1 is hereby maintained.

Summary

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
April 23, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER